Time-Scaled Stochastic Input to Biochemical Reaction Networks

by

Rachel L. Thomas

Department of Mathematics
Duke University

Date: _____

Approved:

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Michael C. Reed, Co-Advisor

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Jonathan C. Mattingly, Co-Advisor

_____
Mauro Maggioni

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Thomas P. Witelski

Dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in the Department of Mathematics
in the Graduate School of Duke University
2010

Abstract

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Abstract

Biochemical reaction networks with a sufficiently large number of molecules may be represented as systems of differential equations. Many networks receive inputs that fluctuate continuously in time. These networks may never settle down to a static equilibrium and are of great interest both mathematically and biologically. Biological systems receive inputs that vary on multiple time scales. Hormonal and neural inputs vary on a scale of seconds or minutes; inputs from meals and circadian rhythms vary on a scale of hours or days; and long term environmental changes (such as diet, disease, and pollution) vary on a scale of years. In this thesis, we consider the limiting behavior of networks in which the input is on a different time scale compared to the reaction kinetics within the network.

We prove analytic results of how the variance of reaction rates within a system compares to the variance of the input when the input is on a different time scale than the reaction kinetics within the network. We consider the behavior of simple chains, single species complex networks, and reversible chains with time-scaled stochastic input as the input speeds up and slows down. In all cases, as the input fluctuates more and more quickly, the variance of species within the system approaches zero. As the input fluctuates more and more slowly, the variance of the species approaches the variance of the input, up to a normalization factor.

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1

Introduction

Biochemical reaction networks with a sufficiently large number of molecules may be represented as systems of differential equations. Many networks receive large inputs that fluctuate continuously in time. When a deterministic system receives stochastic input, the reactions and species within the system will also have stochastic behavior. These networks may never settle down to a static equilibrium and are of great interest both mathematically and biologically. One important question is how the variance of reaction rates within a system compares to the variance of the input. The answer depends on the reaction kinetics, the topology of the network, long-range interactions, and the properties of the input.

As Reed and Nijhout ([13], [12], [16]) have shown, models of cell metabolism can provide insight into biological mechanisms with important medical implications. In these models, the number of molecules is high enough so the biological systems can be approximated by differential equations with stochastic input.

Biological systems receive inputs that vary on multiple time scales. Hormonal and neural inputs vary on a scale of seconds or minutes; inputs from meals and circadian rhythms vary on a scale of hours or days; and long term environmental

changes (such as diet, disease, and pollution) vary on a scale of years. In this thesis, we consider the limiting behavior of networks in which the input is on a different time scale compared to the reaction kinetics within the network.

The biochemical inputs to many biological systems, such as cell metabolism, fluctuate widely in time with the content and frequency of meals, varying activity levels, and environmental factors (refer to [6]). These systems may not have a chance to relax to a steady-state equilibrium. However, cells are able to maintain fairly stable levels of many reaction velocities despite these huge fluctuations in input. A problem of interest is to explore the mathematical mechanisms that enable this stability and how stochastic fluctuations propagate through a system.

For linear, reversible, and non-linear chains, David Anderson ([3],[2]) has proved that the variance of fluxes decreases down the chain. So there is a stabilizing effect in biochemical systems with longer reaction chains. He proved that side reaction systems and feedback loops also lower variance. In weakly reversible single species complex (SSC) systems with mass action kinetics, the variance of species within the system is lower than the variance of the input, after scaling to account for mean values.

Here we are interested in analytic results of how the variance of reaction rates within a system compares to the variance of the input when the input is on a different time scale than the reaction kinetics within the network. I prove limiting results regarding the behavior of simple chains, single species complex networks, and reversible chains with time-scaled stochastic input $\xi_{t/L}$ as the input speeds up and slows down.

Time is scaled by the parameter L and the input is denoted $\xi_{t/L}$. In one limit ($L \to 0$), as the input fluctuates more and more quickly, the variance of species within the system goes to zero. The intuitive idea behind this is that the concentrations of species within a system are found by integrating the input. With quickly fluctuating

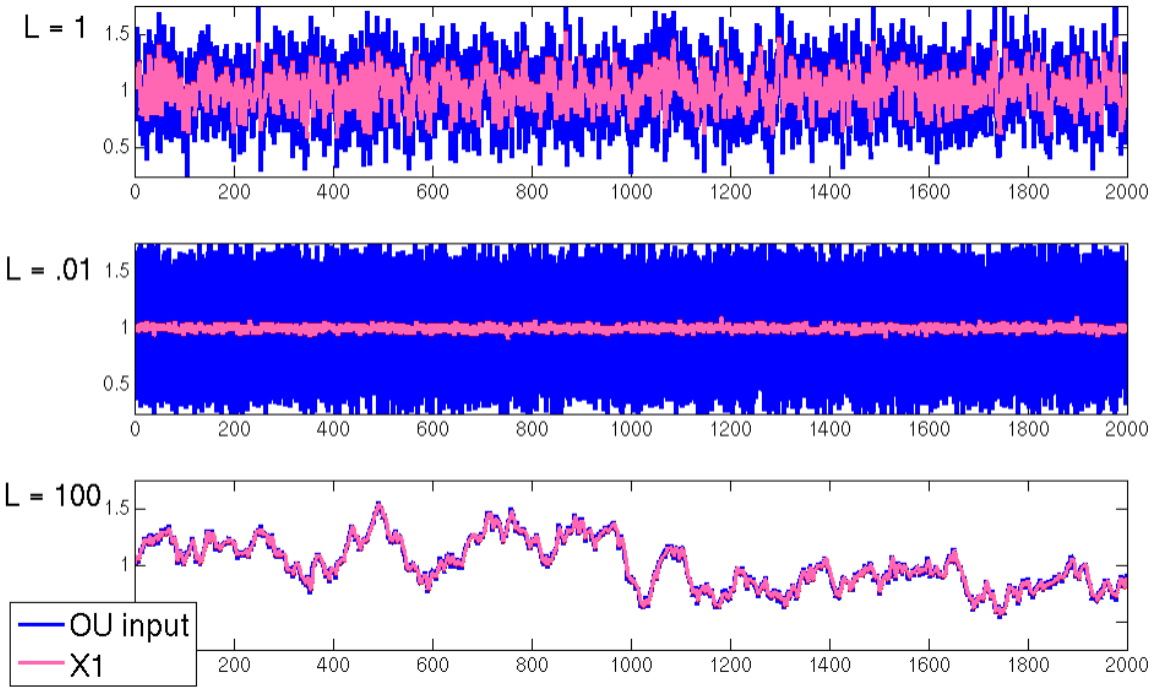


FIGURE 1.1: A numerical simulation of time-scaled Ornstein-Uhlenbeck input to a single species.

input, the fluctuations cancel each other out as they are averaged over. The other limit ($L \to \infty$) is the adiabatic case. As the input fluctuates more and more slowly, the variance of the species approaches the variance of the input. The intuitive reason for this is that although the system is not able to relax completely to equilibrium, the input is changing so slowly that the system is always very near to equilibrium. See Figure 1.1 for the graph of a numerical simulation illustrating these results.

It is assumed that the covariance function of ξ is a measurable, decreasing function $\mathbb{E}[\xi_t \xi_s] = f(|t-s|)$ and that $\lim_{x\to\infty} f(x) = 0$. This means that the process is becoming decorrelated in time, which is a reasonable assumption. The Ornstein-Uhlenbeck process, which has covariance $\frac{1}{2}e^{-|t-s|}$, meets this assumption, whereas Brownian motion, with covariance $min(s,t)$, does not.

In chapter 2, I give an overview of other methods for studying chemical reaction

networks or time-scaled systems and introduce notation. Previous results in the field are discussed, and this work is placed within its larger context.

In chapter 3, I consider the case of a species X_i in a simple chain of linear reactions:

$$\xrightarrow{1+\xi_{t/L}} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{i-1}} X_i \xrightarrow{k_i}$$

I prove that the variance of X_i approaches zero as $L \to 0$ and the variance of X_i approaches the variance of the input as $L \to \infty$. The first order correction terms are calculated. The effect of rate constant magnitude on the variance in a linear chain is also explored. In the case of Ornstein-Uhlenbeck input, I prove that a larger rate constant results in a smaller variance of the flux, but a larger variance of the species concentration.

A commonly studied class of reaction networks is the set of weakly reversible single species complex (SSC) systems with mass action kinetics. These systems can be represented $\frac{d}{dt}\vec{x}(t) = A\vec{x}(t) + \vec{I} + \vec{\xi}_{t/L}$ where A is a matrix of rate constants, $\vec{I} = (I, 0, \ldots, 0)$, and $\vec{\xi} = (\xi, 0, \ldots, 0)$. SSC networks are considered in chapter 4, and I prove that

$$\begin{aligned} \lim_{L\to\infty} \text{Var } X_{i,t}^L &= \left(\frac{m_i}{I}\right)^2 \text{Var } \xi \\ \lim_{L\to 0} \text{Var } X_{i,t}^L &= 0 \end{aligned}$$

where m_i is the mean of the ith species. That is, as $L \to 0$ the variance of X_i approaches zero, and as $L \to \infty$, the variance of X_i approaches the variance of the input, up to a normalization factor.

Reversible chains are a specific type of SSC system:

$$\xrightarrow{I+\xi} X_1 \underset{b_1}{\overset{k_1}{\rightleftharpoons}} X_2 \underset{b_2}{\overset{k_2}{\rightleftharpoons}} \cdots \underset{b_{n-1}}{\overset{k_{n-1}}{\rightleftharpoons}} X_n \xrightarrow{k_n}$$

The result for SSC systems holds for species in the reversible chain. By considering the net flux

$$y_{k-1} = k_{k-1}x_{k-1} - b_{k-1}x_k$$

at each step in the chain, in Chapter 5, I prove the stronger results that

$$\begin{aligned} \lim_{L\to\infty} \text{Var } y_{t,L} &= \text{Var } \xi \\ \lim_{L\to 0} \text{Var } y_{t,L} &= 0 \end{aligned}$$

In Chapter 6, I summarize the results and discuss related open questions of interest. In all of the cases considered in this thesis, as the input speeds up, the variance of the fluxes approaches zero in the limit. Since the input is integrated to calculate concentrations within the system, rapid fluctuations in input cancel one another out as they are averaged over in the integral. As the input slows down, the variance of the species approaches the variance of the input, up to a normalization factor. Although the system never reaches equlibrium, it is able to get very close when the input is incredibly slow. In the slow limit, the system is approximately at equilibrium at all times.

2

Background

This chapter will introduce the mathematical model used to describe chemical reaction networks and review previous results in this field. There is an intrinsic stochasticity to biochemical reactions in the collisions of molecules and the making and breaking of molecular bonds. Systems with a relatively small number of molecules may be modeled as continuous time Markov chains. The state at a given time is a vector $x = (x_1, \ldots, x_n) \in \mathbb{Z}^n_{\geq 0}$ giving the number of molecules of each species. The possible transitions are the possible reactions which may occur. Each reaction is characterized by a rate function $\lambda(x)$, a vector $\nu \in \mathbb{Z}^n_{\geq 0}$ specifying the number of molecules of each species consumed in the reaction, and a vector $\nu' \in \mathbb{Z}^n_{\geq 0}$ specifying the number of molecules of each species created by the reaction. The updated state of the system after the reaction is $x + \nu' - \nu$. As shown in [9], as the volume of discrete reaction models is appropriately scaled up, the limit is a deterministic system of ordinary differential equations. In this work, we consider reaction systems with a large enough number of molecules that they can be modeled continuously.

The biochemistry of reaction systems can be incredibly complex as many of them have long range inhibitions or excitations, the effects of which are difficult to under-

stand. Studying the differential equations poses many challenging questions, such as showing global stability for equilibrium points. Furthermore, there are still stochastic elements in these systems. Since the rate at which enzymes are synthesized can depend on the substrates they are affecting, the parameters may be changing in time. The inputs to biochemical systems may fluctuate widely in time with the content and frequency of meals, changing activity levels, and environmental factors. Such systems may never relax to a static equilibrium, but may still have stationary solutions.

We are interested in understanding the behavior of biochemical systems in cells. One approach is through in silico experimentation with models of actual specific networks. Examples of this can be found in [12], [13], [16], and [17]. All of these papers involve the development of a model of 1-carbon cell metabolism, which includes the folate and methionine cycles and glutathione synthesis. Malfunction of cell metabolism (for instance, through substrate deficits) has been correlated with a host of health problems, including spina bifida, cardiovascular disease, cancer, Alzheimer's disease, Down syndrome, and autism.

The model in [17] (by Reed, Thomas, Pavisic, James, Ulrich, and Nijhout) includes 34 differential equations, one for each substrate represented. Each equation has several Michaelis-Menten terms, and many have inhibition and activation terms. The system is quite complex and highly nonlinear. Since there are several long-range inhibitions and activations, a particular part of the cycle can not be accurately modeled in isolation. See Figure 2.1.

In such computer models, we are interested in qualitative rather than quantitative results. We can decompose the model piece by piece to explore the role that specific reactions, inhibitions, or activations play. Thus, the model can provide new insight into the biological mechanisms at work. We can also experiment with the model by changing inputs or parameters. This allows us to perform tests that it would not be

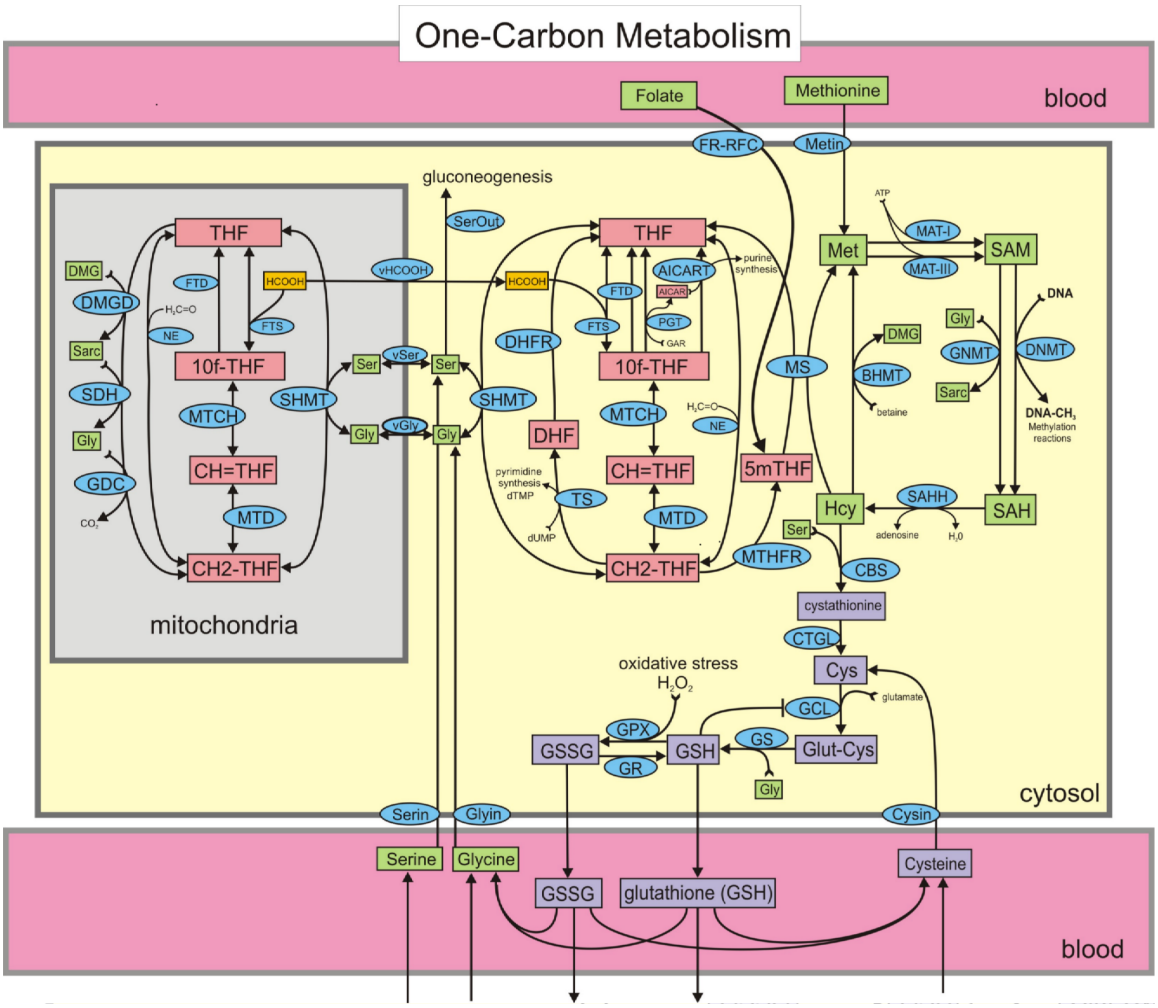


FIGURE 2.1: A model of one-carbon metabolism. Enzymes are denoted by ellipses and substrates are denoted by rectangles.

feasible to perform on people.

Another approach, and the one taken in this thesis, is to study how fluctuations propagate through relatively simple systems. Theorems about how simple systems magnify or suppress fluctuations may provide insight into why more complicated networks are structured as they are.

This type of analysis differs from classical metabolic control analysis (Heinrich and Rapoport, [5], Kacser and Burns, [8]) in that the system here is never at equi-

librium. In metabolic control analysis, a system is at a fixed steady state and a small change is made to one parameter. The system is allowed to relax to a new equilibrium and the partial derivative is then calculated to determine the influence of the changed parameter. The control coefficient is defined

$$\frac{J'}{J} \Big/ \frac{v'}{v}$$

where J is the flux through the system and v is the perturbed parameter, often an enzyme velocity. This gives information about the local behavior near a given steady state, whereas here we are interested in how biochemical systems adapt to continuous large fluctuations in inputs.

Another relevant area of interest is that of linear control theory (refer to [11] and [19]). In control theory, a system receives inputs $u_1(t), \ldots, u_r(t)$, has a set of internal states $x_1(t), \ldots, x_n(t)$, and produces outputs $y_1(t), \ldots, y_m(t)$. The system can be modeled:

$$\begin{cases} \dot{x}(t) &= A(t)x(t) + B(t)u(t) \\ y(t) &= C(t)x(t) \end{cases} \tag{2.1}$$

where A, B, and C are matrices of the appropriate dimensions.

There are several interesting questions. One set of questions is that of *controllability*. Can the system be guided from initial state x_0 to a desired state x_d by modifying the inputs $u(t)$? If so, a cost function for the internal states can be introduced, and it is of interest whether there exists is an optimal control strategy for guiding the system so as to minimize costs. Another set of questions relates to *observability*. Given the values of the outputs y, can the values of the internal states x be inferred? A final set of questions includes those related to *stability*. The system is considered stable if a small perturbation in input results in only a small perturbation of the output.

In stochastic control theory (see [10]), there is a random process x_t^u and a control

function $u(x_t^u, t)$, which determines the probability transition function for x_t^u. The objective of control theory is to specify the control u such that x_t^u possesses some desired property. For instance, this desired property may be that x_t^u will approach some set S with probability one, or that x_t^u will follow as closely as possible some pre-assigned path. Alternately, there may be the goal of choosing u so as to minimize some cost function associated with x_t^u,

$$C^u(x) = \mathbb{E}b(x_{\tau_u}) + \mathbb{E}\int_0^{\tau_u} k(x_s^u, u_s)ds,$$

where τ_u is a random arrival time to some set S. Similar questions may be asked as in stochastic control theory as in deterministic control theory, such as questions of the existence or uniqueness of a control, the existence of uniquenss of an optimal control given a cost function, and whether the system is stable.

Although control theory is most commonly used in engineering and operations research, it could also have applications to biochemical reaction networks. Many biochemical systems, such as cell metabolism (see [13], [16], and [17]), have a range of medical implications, and irregular metabolic profiles are correlated with a variety of diseases. Thus, it would be of interest to determine how to raise or lower the concentration of a particular substrate, without adversely affecting the concentrations of other substrates, by modifying the inputs. In the case of cell metabolism, the inputs are amino acids, which are received through food and possibly vitamin supplements. Potential applications of control theory to biochemical modeling are discussed further in the conclusion.

In this work, we are primarily interested in exogenous stochastic forcing of systems of differential equations. This stochastic forcing may occur on varying time scales, since many biological systems operate on multiple time scales. For instance, hormonal and neural inputs vary on a scale of seconds or minutes; inputs from meals and circadian rhythms vary on a scale of hours or days; and long term environmental

changes (such as diet, disease, and pollution) vary on a scale of years. We consider the limiting behavior of networks in which the input is on a different time scale compared to the reaction kinetics within the network.

In [14], Pavliotis and Stuart consider systems with multiple time scales. A prototypical example is the system:

$$\begin{cases} \frac{dx}{dt} &= f(x,y) \\ \frac{dy}{dt} &= \frac{1}{\epsilon}g(x,y) + \frac{1}{\sqrt{\epsilon}}\beta(x,y)\frac{dW}{dt} \end{cases} \tag{2.2}$$

where $\epsilon \ll 1$. Here, x is the slow variable and y is the fast variable. By averaging over the invariant distribution for y, the variable y can be eliminated and the x variable can be approximated by an equation $\frac{dX}{dt} = F(X)$. The effective equation does not contain the parameter ϵ and is thus more tractable to numerical solution or analysis.

In general, multiscale systems have generators of the form

$$\mathcal{L}^\epsilon = \frac{1}{\epsilon}\mathcal{L}_0 + \mathcal{L}_1 \quad \text{or} \quad \mathcal{L}^\epsilon = \frac{1}{\epsilon^2}\mathcal{L}_0 + \frac{1}{\epsilon}\mathcal{L}_1 + \mathcal{L}_2$$

depending on whether there are two or three time scales present. The evolution of $\frac{\partial u^\epsilon}{\partial t} = \mathcal{L}^\epsilon u^\epsilon$ is of interest. Using formal perturbation expansions, effective equations can be derived that approximate the behavior of the system. These methods are applied to ODEs (via the method of characteristics), Markov chains (via the forward equation), SDEs (via the Kolmogorov equation), transport PDEs, and parabolic PDEs.

A chemical reaction network is a chemical system with multiple chemical species and multiple reactions. Chemical reaction networks may be modeled a systems of ODEs, SDEs, or PDEs or as Markov chains, depending on the volume, kinetics, and inputs of the systems.

As mentioned earlier, when the number of molecules is relatively low, the reaction network can be modeled as a continuous time Markov Chain. The states are vectors

indicating the number of molecules of each species, and the reactions are modeled as the possible transitions for the chain. The kth reaction is determined by a vector of inputs ν_k specifying the number of molecules consumed in the reaction, a vector ν'_k specifying the number of molecules created by the reaction, and a function $\lambda_k(x)$ of the state x that gives the rate at which the reaction occurs. In many cases, some species in the network are present in much higher concentrations than others, and reaction rate constants may vary over several orders of magnitude.

The question of simulating systems with multiple scales is of mathematical and practical interest. In [4], E, Liu, and Vanden-Eijnden present a simulation algorithm for discrete chemical kinetic systems with multiple time scales. Simulating the entire system with a uniform time step would result in most of the computational cost being spent on the fast reactions, which are often of less interest. The slow processes are generally the rate limiting steps and of greater interest.

The main idea of the nested algorithm is to use an outer stochastic simulation algorithm (SSA) to simulate the slow processes with rates computed from an inner SSA which simulates the fast reactions. An inner SSA first runs independent replicas of the process using only the fast reactions. The results are used to compute modified slow reaction rates which are the rates for the outer SSA. These steps are then iterated. The fast processes have effectively been averaged out.

The nested SSA is an approximate realization of the system. In order to calculate the error tolerance, *slow variables* are defined as linear functions of species that are invariant under the fast reactions. Since each species may be involved in both fast and slow reactions, there are not necessarily any "slow species". In practice, the slow variables may not be explicitly known. However, their existence is used in proving the theoretical error bound. The algorithm can be generalized to multilevel SSA for systems with more than two time scales and to an adaptive SSA for systems in which the set of fast reactions changes as the process progresses. Note that this algorithm

is specific to discrete systems and would not work for ODEs or SDEs.

In this work, we are interested in chemical systems with large enough volume to be modeled by systems of differential equations. We will now make our notation more formal and introduce some of the types of reaction networks that we consider here.

Definition 2.0.1. *A* **chemical reaction network** *may be represented as a directed graph along with a triple* $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ *of the species, complexes, and reactions. Each node of the graph corresponds to a chemical species, and a directed edge corresponds to a reaction.*

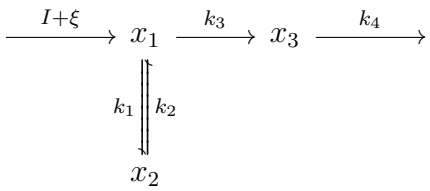
Letting m be the number of species, the vectors of concentrations are elements of $\mathbb{R}^m_{\geq 0}$. Each vertex of the graph is a linear combination of species with non-negative integer coefficients, that is, a chemical complex. The reactions are directed edges between complexes. For instance, $C_1 \to C_2$ is a reaction transforming reactant C_1 into product C_2. The zero complex is used to denote inputs and outputs to the network. For $r = C_1 \to C_2 \in \mathcal{R}$, the associated reaction vector is $C_2 - C_1 \in \mathbb{R}^m$. The stoichiometric subspace $\mathcal{S}$ of a chemical reaction network is the span of the reaction vectors in the network. If $x - y \in \mathcal{S}$ for two species vectors $x, y \in \mathbb{R}^m_{\geq 0}$, then we say that x and y are stoichiometrically compatible and in the same stoichiometric compatibility class. Stoichiometric compatibility classes form an equivalence relation on $\mathcal{S}$. For deterministic systems, the question of interest is not whether a given system has a unique fixed point, but whether within each stoichiometric compatibility class there is a unique fixed point. Similarly, for stochastically modeled systems, it is of interest to compute stationary distributions for each closed, irreducible subset of the state space (each of which is contained within a stoichiometric compatibility class).

Definition 2.0.2. *A* **chemical reaction system** *is represented* $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\,\mathcal{K}\}$ *where*

$\mathcal{K}$ denotes the kinetics of the system. So $\mathcal{K}$ consists of functions $\{F_r(x)\}$ for each reaction $r \in \mathcal{R}$.

We can represent $\dot{x}(t) = \Sigma_{r\in\mathcal{R}} F_r(x(t))v_r$ where for reaction r, v_r is the associated reaction vector and F_r the associated rate function.

In this thesis, we are primarily interested in reactions with mass action kinetics. These are reactions $\alpha_1 x_1 + \ldots + \alpha_m x_m \rightarrow \beta_1 x_1 + \ldots + \beta_m x_m$ with kinetics $F(x_1, \ldots, x_m) = k x_1^{\alpha_1} \ldots x_m^{\alpha_m}$ where $k > 0$. In chapter 5, we will consider some nonlinear systems, including Michaelis-Menten kinetics. In all cases, the reaction function depends only on substrates in the reactant complex and not on substrates in the product complex. For simplicity, if a system has mass action kinetics, we will label the edges in the diagram with the rate constants rather than the rate funtions. Below is a simple example to illustrate the notation:



Here there are three chemical species, $\mathcal{S} = \{x_1, x_2, x_3\}$. Each complex consists of a single species in this case so $\mathcal{C} = \{x_1, x_2, x_3\}$. Species x_1 receieves a constant input I and a stochastic input ξ_t. Species x_1 is transformed into x_2 at rate k_1 proportional to itself. Species x_2 is transformed back into x_1 at rate k_2 proportional to itself. There are four reactions in total, $\mathcal{R} = \{x_1 \rightarrow x_2,\ x_1 \rightarrow x_3,\ x_2 \rightarrow x_1,\ x_3 \rightarrow 0\}$. The chemical species can be represented as the vector $x(t) = (x_1(t), x_2(t), x_3(t))$. The input vector has a non-zero constant in the first place and zeros elsewhere, $\vec{I} = (I, 0, 0)$. The stochastic forcing is applied only to species x_1. For simplicity of notation, we let $\vec{\xi}(t)$ denote $(\xi(t), 0, 0)$. Then the system can be represented by differential equation 2.3.

$$\begin{cases} \dot{x}(t) &= Ax(t) + \vec{I} + \vec{\xi}(t) \\ x(0) &= x_0 \end{cases} \tag{2.3}$$

where A is the matrix of rate constants:

$$A = \begin{pmatrix} -(k_1 + k_3) & k_2 & 0 \\ k_1 & -k_2 & 0 \\ k_3 & 0 & -k_4 \end{pmatrix}$$

Deficiency zero networks are a class of chemical reaction systems studied in [1]. Although deficiency zero systems are defined by network properties, results can be proved concerning their dynamical properties.

Definition 2.0.3. *The* **deficiency** *of a chemical reaction network is $\delta = |\mathcal{C}| - l - s$, where $|\mathcal{C}|$ is the number of complexes, l is the number of linkage classes (connected components), and s is the dimension of the stoichiometric subspace of the network.*

The correct question is not if there is a unique fixed point for a given deterministic system, but rather, if within each stoichiometric compatibility class there is a unique fixed point. For stochastically modeled systems, it is of interest to compute stationary distributions for each closed irreducible subset of the state space (each of which is contained within a stoichiometric compatibility class).

Theorem 2.0.1. Deficiency Zero Theorem *Given a weakly reversible deficiency zero network*

$$\begin{aligned} x(t) &= x(0) + \Sigma_k \Big(\int_o^t f_k(x(s))ds \Big)(\nu'_k - \nu_k) \\ &=: x(0) + \int_0^t f(x(s))ds \\ f_k(x) &= \kappa_k x_1^{\nu_{1k}} x_2^{\nu_{2k}} \dots x_m^{\nu_{mk}} \end{aligned}$$

Then for any choice of rate constants κ_k, within each positive stoichiometric compatibility class there is precisely one equilibrium value and that equilibrium value is locally asymptotically stable relative to its compatibility class.

One class of chemical reaction networks studied by David Anderson, [3], is the class of single species complex (SSC) systems. One condition on these networks is that each chemical reaction converts one substrate into one product. That is, multiple species do not combine to form a product, and one reaction can not produce multiple products.

Definition 2.0.4. *A graph is* **weakly reversible** *if whenever there is a directed path form X_i to X_j, then there is also a directed path from X_j to X_i. A system with non-zero input is called* **weakly reversible** *if it is weakly reversible in the above sense and there is at least one non-zero output.*

Assume that the graph is connected, and that the reaction rate is proportional to the reactant species (mass action kinetics) with non-negative rate constants.

Definition 2.0.5. *A* **single species complex network** *is a network that:*

1. *is weakly reversible*
2. *has mass action kinetics*
3. *consists of a single linkage class*
4. *each complex is a single substrate*

It is from the last property that the name is derived.

Such systems can be represented as in equation 2.3 and have a stationary solution. Below, we will let $\vec{I} = (I, 0, \ldots, 0)$ and $\vec{\xi}(t) = (\xi(t), 0, \ldots, 0)$.

Theorem 2.0.2. *(Anderson [3]) Consider a weakly reversible SSC system with mass action kinetics, nonzero input vector $\vec{I}$ and a mean zero, finite variance, stationary stochastic input $\xi(t) \geq -I$ represented as*

$$\begin{cases} \frac{d}{dx}\vec{x}(t) &= A\vec{x}(t) + \vec{I} + \vec{\xi}(t) \\ \vec{x}(0) &= \vec{x_0} \end{cases} \tag{2.4}$$

Then the process $\vec{x}^*(t) = \vec{x}^*(t, \xi)$ defined by

$$\vec{x}^*(t, \xi) = \int_{-\infty}^{t} e^{A(t-s)}\vec{I}ds + \int_{-\infty}^{t} e^{A(t-s)}\vec{\xi}(s)ds \tag{2.5}$$

is the unique stationary solution.

Intuitively, a unique stationary measure means that at large times, the joint distribution of concentration values becomes independent of time and independent of the initial conditions. That is, the concentration values converge to an equilibrium distribution.

Using this stationary solution, Anderson proves that the variance of any species within an SSC system is strictly less than the variance of the input, up to a normalization factor.

Theorem 2.0.3. *(Anderson, [3]) Let $x^*(t)$ be the solution of an SSC system with one input $\vec{I} + \vec{\xi}(t)$, where $\xi(t)$ is a stationary stochastic process with finite variance, mean zero, and $\xi(t) \geq -I$. Let m_i be the mean of species x_i. Then*

$$var(x_i^*) < \left(\frac{m_i}{I}\right)^2 Var(\xi)$$

Proof.

$$\begin{aligned}
Var(x_i^*(t)) &= \mathbf{E}\left(\int_{-\infty}^{t} \xi(s)e^{A(t-s)}e_1 \cdot e_i ds\right)^2 \\
&= \mathbf{E}\left(\int_{-\infty}^{t} \xi(s)(e^{A(t-s)}e_1 \cdot e_i)^{1/2}(e^{A(t-s)}e_1 \cdot e_i)^{1/2} ds\right)^2 \\
&< \mathbf{E}\left(\int_{-\infty}^{t} \xi(s)^2 e^{A(t-s)}e_1 \cdot e_i ds\right)\left(\int_{-\infty}^{t} e^{A(t-s)}e_1 \cdot e_i ds\right) \\
&= Var(\xi)\left(\int_{-\infty}^{t} e^{A(t-s)}e_1 \cdot e_i ds\right)^2 \\
&= \left(\frac{m_i}{I}\right)^2 Var(\xi)
\end{aligned}$$

□

Applying this theorem to the particular case of a nonreversible chain with mass action kinetics yields the result that variance decreases down a chain.

$$\xrightarrow{I+\xi(t)} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{m-1}} X_m \xrightarrow{k_m}$$

Theorem 2.0.4. *(Anderson, [3]) For a non-reversible chain and stationary stochastic process $\xi(t)$ with finite variance, mean zero, and $\xi(t) \geq -I$,*

$$\begin{aligned}
Var(k_i x_i^*) &< Var(\xi) \\
Var(k_{i+1}x_{i+1}^*) &< Var(k_i x_i^*)
\end{aligned}$$

Proof. Consider the input to $k_{i+1}x_{i+1}^*$ to be $I + (k_i x_i^* - I)$. Then $\psi = (k_i x_i^* - I)$ is a finite variance, mean zero, stationary stochastic process By theorem 2.0.3, $Var(k_{i+1}x_{i+1}^*) < Var(k_i x_i^*)$. □

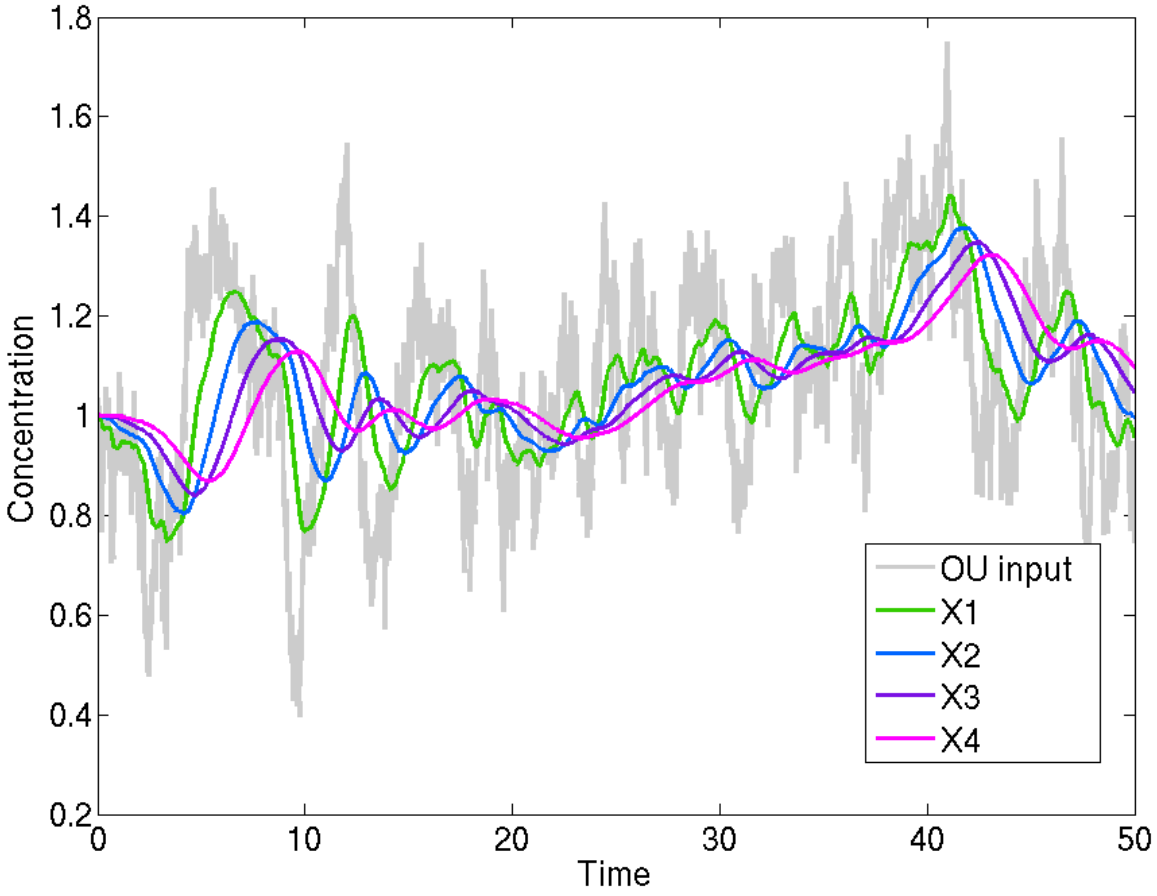


FIGURE 2.2: In a simulation of a chain given Ornstein-Uhlenbeck stochastic input, the variance of the fluxes decreases as one proceeds down the chain.

The results of a computational simulation of a chain with stochastic input are shown in Figure 2.2. Notice that the amplitude of the fluctuations decreases for each subsequent species down the chain. There is also a phase shift, as it takes time for the fluctuations to propagate down the chain. Once the input changes, it takes a little bit of time for X_1 to adjust. It then takes time for X_2 to respond to the change in X_1, before X_3 can adjust to the change in X_2, and so on. Having many intervening biochemical steps between an input and an output has a stabilizing effect on the flux of the output.

Anderson showed that side reaction systems and positive feedback loops are also

mechanisms for lowering variance. A side reaction system of a chain is any SSC system that both receives its input from and has its output flow back to the same species on the chain.

$$\begin{array}{c} \xrightarrow{I+\xi(t)} X_1 \xrightarrow{k_1} \\ {\scriptstyle k_2}\big\uparrow\big\downarrow{\scriptstyle k_3} \\ \boxed{\text{Side System}} \end{array} \tag{2.6}$$

A chain with a side reaction has a lower variance than the comparable chain without the side system.

$$\xrightarrow{I+\xi(t)} \tilde{X}_1 \xrightarrow{k_1} \tag{2.7}$$

Theorem 2.0.5. *(Anderson, [3]) Assume that ξ is a stochastic process such that for $s < t$, $\mathbf{E}\xi(t)\xi(s) > 0$ and $\mathbf{E}\xi(t)\xi(s)$ is increasing in s. Assume also that ξ has mean zero and finite variance and that $\xi_t \geq -I$. Let x_1^* be the stationary solution for node X_1 in 2.6 and let $\tilde{x}_1^*$ be the stationary solution for node $\tilde{X}_1$ in 2.7 Then the chain with the side reaction system has lower variance:*

$$Var(k_1 x_1^*) < Var(k_1 \tilde{x}_1^*)$$

A feedback loop is an SSC system that recieves input from one species of a chain and sends its output to an earlier species of that chain.

$$\begin{array}{c} \xrightarrow{I+\xi(t)} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{n-1}} X_n \xrightarrow{k_n} \\ {\scriptstyle f_1(t)}\nwarrow \qquad \swarrow{\scriptstyle c} \\ \boxed{\text{Subsystem}} \end{array} \tag{2.8}$$

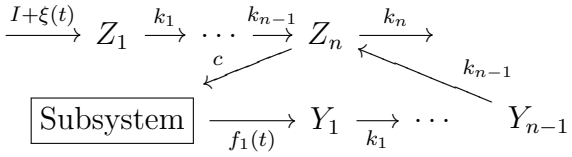
Compared to a chain with the same rate constants but without the feedback loop, the variance of the flux out of the chain with the feedback loop is lower.

$$\xrightarrow{I+\xi(t)} \tilde{X}_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{n-1}} \tilde{X}_n \xrightarrow{k_n} \tag{2.9}$$

Theorem 2.0.6. *(Anderson, [3]) Assume that ξ is a stochastic process such that for $s < t$, $\mathbf{E}\xi(t)\xi(s) > 0$ and $\mathbf{E}\xi(t)\xi(s)$ is increasing in s. Assume also that ξ has mean zero and finite variance and that $\xi_t \geq -I$. Let x_1^* be the stationary solution for node X_1 in 2.8 and let $\tilde{x}_1^*$ be the stationary solution for node $\tilde{X}_1$ in 2.9 Then the flux out of the chain with the feedback loop has lower variance:*

$$Var(k_n x_n^*) < Var(k_n \tilde{x}_n^*)$$

Proof. The chain with feedback loop in 2.8 can be converted into a chain with a side system as follows:



where

$$\begin{aligned} X_i &= Y_i + Z_i \text{ for } 1 \leq i \leq n-1 \\ X_n &= Z_n \end{aligned}$$

Theorem 2.0.5 can now be applied to prove the desired result. □

In [2], Anderson and Mattingly prove that the result of decreased variance down a chain still holds when the assumptions of mass action kinetics and single species complexes are dropped.

$$\xrightarrow{I+\xi(t)} X_1 \xrightarrow{F_1} X_2 \xrightarrow{F_2} \cdots \xrightarrow{F_{n-1}} X_n \xrightarrow{F_n}$$

Theorem 2.0.7. *(Anderson and Mattingly, [2]) Consider a chain with non-linear kinetics F_i such that*

1. $F_i(0) = 0$

2. $F_i'(x) > 0$, *for all* $x \in \mathbb{R}_{>0}$

3. $\lim_{x \to \infty} F_i(x) > I$

where the stochastic input is either a white noise term that turns off if x_1 *approaches zero, or a mean zero, finite variance, stationary process. Let* $x^*(t)$ *be the stationary solution. Then for all* $1 \leq i \leq n$ *and all* t

$$Var\ F_i(x_i^*(t)) > Var\ F_{i+1}(x_{i+1}^*(t))$$

They also generalize this result to the case where each complex may consist of multiple species, as long as no species is contained in more than one complex. For instance, the following chain fits this criteria, assuming that the partial derivatives of the F_i are positive.

$$\xrightarrow{I+\xi(t)} X_1^1 + 2X_1^2 \xrightarrow{F_1(X_1^1, X_1^2)} 3X_2^1 \xrightarrow{F_2(X_2^1)}$$

3

Simple Chains

In this chapter we consider the limiting behavior of simple chains with linear kinetics and time-scaled stochastic input.

$$\xrightarrow{I+\xi_{t/L}} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{m-1}} X_m \xrightarrow{k_m}$$

Specifically, we're interested in the limit of $\mathrm{Var}(k_i X_i)$ as the stochastic input $\xi_{t/L}$ speeds up ($L \to 0$) or slows down ($L \to \infty$). We will consider only stochastic input that is becoming decorrelated in time, which is a reasonable assumption for biological processes. Furthermore we will require that the input remain non-negative.

In section 3.1 we will prove the result for the first step of the chain. In section 3.2, we inductively prove the result for all species in a chain. In section 3.3, we find the first order correction terms.

Assumption 3.0.1. *Let ξ be a stochastic process such that:*

1. $\xi_t \geq -I$ *and* $\mathbb{E}\xi = 0$
2. $\mathbb{E}(\xi_t \xi_s) = f(|t-s|)$ *where $f \geq 0$ is measurable and bounded with* $\lim_{x\to\infty} f(x) = 0$.

To simplify our calculations, we will define the covariance function f on the negatives by letting it be an even function, that is $f(-x) = f(x)$. Assume $f(x) \leq M$ for all x.

3.1 First Step of the Chain

We consider the equations for a one step chain:

$$\begin{cases} dX_t^L &= Idt + \xi_{t/L}dt - kX_t^L dt \\ X_0 &= I \end{cases} \tag{3.1}$$

$$\xrightarrow{I+\xi_{t/L}} X \xrightarrow{k}$$

The solution to equation 3.1 is

$$X_t^L = \frac{I}{k} + \int_{-\infty}^{t} e^{-k(t-s)}\xi_{s/L}ds \tag{3.2}$$

Since $\int_{-\infty}^{t} e^{-t+s}ds = 1$, the variance of the stochastic input can be rewritten as:

$$\text{Var } \xi = \mathbb{E}(\xi_t\xi_t) = f(0) = \int_{-\infty}^{t}\int_{-\infty}^{t} e^{-2t+s+r}f(0)dsdr \tag{3.3}$$

Theorem 3.1.1. *For equation 3.1 where the stochastic process meets assumption 3.0.1, the limiting behavior as the input slows down is*

$$\lim_{L\to\infty} \text{Var } kX_t^L = f(0) = \text{Var } \xi$$

Proof. We are interested in the variance of the first node X_t. We simplify its expres-

sion by using a change of variable:

$$\begin{aligned}
\text{Var } X_{t,L} &= \mathbb{E}\Big[\int_{-\infty}^{t} e^{-k(t-s)}\xi_{s/L}ds\Big]^2 \\
&= \mathbb{E}\Big[\int_{-\infty}^{t} e^{-k(t-s)}\xi_{s/L}ds \int_{-\infty}^{t} e^{-k(t-r)}\xi_{r/L}dr\Big] \\
&= \int_{-\infty}^{t}\int_{-\infty}^{t} e^{k(-2t+s+r)}\mathbb{E}[\xi_{s/L}\xi_{r/L}]dsdr \\
&= \int_{-\infty}^{t}\int_{-\infty}^{t} e^{k(-2t+s+r)} f\Big(\frac{1}{L}|s-r|\Big)dsdr \\
&= \int_{-\infty}^{t}\int_{-\infty}^{t-r} e^{k(-2t+v+2r)} f\Big(\frac{v}{L}\Big)dvdr
\end{aligned}$$

Switching the order of integration,

$$\begin{aligned}
&= \int_{-\infty}^{0}\int_{-\infty}^{t} e^{k(-2t+v+2r)} f\Big(\frac{v}{L}\Big)drdv + \int_{0}^{\infty}\int_{-\infty}^{t-v} e^{k(-2t+v+2r)} f\Big(\frac{v}{L}\Big)drdv \\
&= \frac{1}{2k}\int_{-\infty}^{0} e^{kv} f\Big(\frac{v}{L}\Big)dv + \frac{1}{2k}\int_{0}^{\infty} e^{-kv} f\Big(\frac{v}{L}\Big)dv \\
&= \frac{1}{k}\int_{0}^{\infty} e^{-kv} f\Big(\frac{v}{L}\Big)dv \qquad (3.4)
\end{aligned}$$

In order to evaluate the limit of the variance, we will need to use the Dominated Convergence Theorem (for instance, see [20]).

Theorem 3.1.2. *(Lebesgue Dominated Convergence Theorem) Let g be integrable over E, and suppose that $< f_n >$ is a sequence of measurable functions such that on E*

$$|f_n(x)| \leq g(x)$$

and such that almost everywhere on E

$$f_n(x) \to f(x).$$

Then

$$\int_E f(x)dx = \lim_{n\to\infty} \int_E f_n(x)dx.$$

We first define:

$$\begin{aligned} g_L(v) &= e^{-kv} f(\frac{v}{L}) \\ g(v) &= Me^{-kv} \end{aligned}$$

Since f is measurable, g_L is measurable on $[0, \infty)$. Also, g is integrable:

$$\int_0^\infty e^{-kv} M dv = \frac{M}{k}$$

Thus, because $g_L \leq g$ and g is integrable, we can use the Dominated Convergence Theorem to take the limits as L goes to zero and as L goes to infinity.

Applying the Dominated Convergence Theorem to 3.4, we obtain:

$$\begin{aligned} \lim_{L\to\infty} \text{Var } X_t^L &= \lim_{L\to\infty} \frac{1}{k} \int_0^\infty e^{-kv} f\Big(\frac{v}{L}\Big) dv \\ &= \int_0^\infty \lim_{L\to\infty} \frac{1}{k} e^{-kv} f\Big(\frac{v}{L}\Big) dv \\ &= \frac{1}{k} \int_0^\infty e^{-kv} f(0) dv \\ &= \frac{f(0)}{k^2} \end{aligned}$$

Thus, $\lim_{L\to\infty} \text{Var } kX_t^L = f(0)$. □

Now consider the case where the input is speeding up, that is $L \to 0$.

Theorem 3.1.3. *For equations 3.1 where the stochastic process follows 3.0.1, the limiting behavior as the input slows down is:*

$$\lim_{L\to 0} \text{Var } \ kX_t^L = 0$$

Proof. The calculation of the limit as L approaches 0 is slightly more complicated than the L to ∞ case because we need to break the integral up into two regions. Beginning with equation 3.4, we fix $\epsilon > 0$ and use the Dominated Convergence Theorem:

$$\begin{aligned}
\lim_{L\to 0} \text{Var } X_t^L &= \lim_{L\to 0} \frac{1}{k} \int_0^\infty e^{-kv} f\Big(\frac{v}{L}\Big) dv \\
&= \lim_{L\to 0} \frac{1}{k} \Big[\int_0^\epsilon e^{-kv} f\Big(\frac{v}{L}\Big) dv + \int_\epsilon^\infty e^{-kv} f\Big(\frac{v}{L}\Big) dv \Big] \\
&= \lim_{L\to 0} \frac{1}{k} \int_0^\epsilon e^{-kv} f\Big(\frac{v}{L}\Big) dv + \frac{1}{k} \int_\epsilon^\infty \lim_{L\to 0} e^{-kv} f\Big(\frac{v}{L}\Big) dv
\end{aligned}$$

By assumption 3.0.1, $\lim_{x\to\infty} f(x) = 0$ and $f(x)$ is bounded by M.

$$\begin{aligned}
\lim_{L\to 0} \text{Var } X_t^L &= \lim_{L\to 0} \frac{1}{k} \int_0^\epsilon e^{-kv} f\Big(\frac{v}{L}\Big) dv + 0 \\
&\leq \lim_{L\to 0} \frac{1}{k} \int_0^\epsilon e^{-kv} M dv \\
&= \frac{M}{k^2}(1 - e^{-k\epsilon})
\end{aligned}$$

Since $\epsilon > 0$ was arbitrary and variance is non-negative, $\lim_{L\to 0} \text{Var } X_t^L = 0$. □

3.2 Down the Chain

The previous limiting results also hold for node X_i in a longer chain.

$$\xrightarrow{1+\xi_{t/L}} X_1 \xrightarrow{k_1} \cdots \xrightarrow{k_{i-1}} X_i \xrightarrow{k_i}$$

Theorem 3.2.1. *Given assumption 3.0.1 and a linear chain,*

$$\begin{aligned}
\lim_{L\to\infty} \text{Var } k_i X_{i,t}^L &= \text{Var } \xi \\
\lim_{L\to 0} \text{Var } k_i X_{i,t}^L &= 0
\end{aligned}$$

Proof. We can inductively apply Theorems 3.1.1 and 3.1.3. First, however, we must prove that the input $k_1 X_1$ has the same form as the original input $1 + \xi_{t/L}$.
In the stationary solution, flow in must equal flow out and so

$$\mathbb{E}[k_1 X_1] = \mathbb{E}[I + \xi_{t/L}] = I$$

Recall equation 3.1,

$$X_{1,t} = \frac{1}{k_1} + \int_{-\infty}^{t} e^{-k_1(t-s)} \xi_s ds$$

We calculate the covariance by using a change of variable and switching the order of integration.

$$\begin{aligned}
\mathrm{Cov}(X_t X_r) &= \mathbb{E}\Big[\int_{-\infty}^{t} e^{-k(t-s)} \xi_s ds \int_{-\infty}^{r} e^{-k(r-u)} \xi_u du \Big] \\
&= \int_{-\infty}^{r} \int_{-\infty}^{t} e^{-k(t+r-s-u)} f(|s-u|) ds du \\
&= \int_{-\infty}^{r} \int_{-\infty}^{t-u} e^{-k(t+r-v-2u)} f(v) dv du \\
&= \int_{-\infty}^{t-r} \int_{-\infty}^{r} e^{-k(t+r-v-2u)} f(v) du dv + \int_{t-r}^{\infty} \int_{-\infty}^{-v+t} e^{-k(t+r-v-2u)} f(v) du dv
\end{aligned}$$

Evaluating the integrals, we simplify:

$$\begin{aligned}
\mathrm{Cov}(X_t X_r) &= \frac{1}{2k} \int_{-\infty}^{t-r} e^{-k(t-r-v)} f(v) dv + \frac{1}{2k} \int_{t-r}^{\infty} e^{-k(-t+r+v)} f(v) dv \\
&= \frac{1}{2k} \int_{r-t}^{\infty} e^{-k(t-r+v)} f(v) dv + \frac{1}{2k} \int_{t-r}^{\infty} e^{-k(-t+r+v)} f(v) dv \\
&= \frac{1}{2k} e^{k(r-t)} \int_{r-t}^{\infty} e^{-kv} f(v) dv + \frac{1}{2k} e^{k(t-r)} \int_{t-r}^{\infty} e^{-kv} f(v) dv
\end{aligned}$$

The covariance equation of X_1 can be defined

$$\begin{aligned}\tilde{f}(|t-r|) &= \frac{1}{2k}e^{k|t-r|}\int_{|t-r|}^{\infty}e^{-kv}f(v)dv + \frac{1}{2k}e^{-k|t-r|}\int_{-|t-r|}^{\infty}e^{-kv}f(v)dv \\ \tilde{f}(x) &= \frac{1}{2k}e^{kx}\int_{x}^{\infty}e^{-kv}f(v)dv + \frac{1}{2k}e^{-kx}\int_{-x}^{\infty}e^{-kv}f(v)dv\end{aligned}$$

We can evaluate the limit of $\tilde{f}(x)$ as x tends to infinity to confirm that X_1 meets the conditions of our reasonable stochastic processes as defined in the previous section.

First, fix a value y such that $0 < y < x$. We will use the fact that f is an even function and montone decreasing as $|x|$ increases, with $\lim_{x\to\infty} f(x) = 0$.

$$\begin{aligned}\lim_{x\to\infty}\tilde{f}(x) &= \lim_{x\to\infty}\frac{1}{2k}e^{kx}\int_{x}^{\infty}e^{-kv}f(v)dv + \frac{1}{2k}e^{-kx}\int_{-x}^{\infty}e^{-kv}f(v)dv \\ &\leq \lim_{x\to\infty}\left[\frac{f(x)}{2k}e^{kx}\int_{x}^{\infty}e^{-kv}dv + \frac{f(y)}{2k}e^{-kx}\int_{-x}^{-y}e^{-kv}dv + \right. \\ &\qquad \left.\frac{f(0)}{2k}e^{-kx}\int_{-y}^{0}e^{-kv}dv + \frac{f(0)}{2k}e^{-kx}\int_{0}^{\infty}e^{-kv}dv\right] \\ &\leq \lim_{x\to\infty}\left[\frac{f(x)}{2k^2}e^{kx}(e^{-kx}-0) + \frac{f(y)}{2k^2}e^{-kx}(e^{kx}-e^{ky}) + \right. \\ &\qquad \left.\frac{f(0)}{2k^2}e^{-kx}(e^{ky}-1) + \frac{f(0)}{2k^2}e^{-kx}(1-0)\right] \\ &\leq \lim_{x\to\infty}\left[\frac{f(x)}{2k^2} + \frac{f(y)}{2k^2}(1-e^{k(-x+y)}) + \right. \\ &\qquad \left.\frac{f(0)}{2k^2}(e^{k(-x+y)}-e^{-kx}) + \frac{f(0)}{2k^2}e^{-kx}\right] \\ &= \frac{f(y)}{2k^2}\end{aligned}$$

However, since y can be arbitrarily large and $\lim_{x\to\infty} f(x) = 0$, we have that $\lim_{x\to\infty}\tilde{f}(x) \leq \frac{f(y)}{2k^2} \to 0$. The covariance of X_1 fulfills assumption 3.0.1 and we can

inductively apply Theorems 3.1.1 and 3.1.3. □

3.3 First Order Correction Terms

For the case where L approaches infinity, we can use the Taylor expansion of f around 0 to find the correction terms.

$$\begin{aligned}
\text{Var } X_t^L &= \int_0^\infty e^{-v} f\Big(\frac{v}{L}\Big) dv \\
&= \int_0^\infty e^{-v} \big[f(0) + \frac{v}{L} f'(0) + \frac{v^2}{2L^2} f''(0) + \ldots \big] dv \\
&= f(0) \int_0^\infty e^{-v} dv + \frac{1}{L} f'(0) \int_0^\infty v e^{-v} dv + \frac{1}{2L^2} f''(0) \int_0^\infty v^2 e^{-v} + \ldots \\
&= f(0) + \frac{1}{L} f'(0) + \frac{1}{L^2} f''(0) + \ldots
\end{aligned}$$

For the case where L approaches zero, we will need the additional assumption that f has $k \geq 2$ finite moments. Then we can use the Taylor expansion with remainder:

$$e^{-Lw} = 1 - Lw + \frac{(Lw)^2}{2!} - \frac{(Lw)^3}{3!} + \ldots + \frac{(-\xi)^k e^{-\xi}}{k!} (-Lw)^k$$

where ξ is between 0 and Lw (so ξ depends on w).

The remainder term can be bounded by $\frac{k^k e^{-k}}{k!}(Lw)^k$, since the maximum of $\frac{\xi^k e^{-\xi}}{k!}$ occurs at $\xi = k$. Note that the sign of the remainder is always positive since $(-\xi)^k (-Lw)^k = (-1)^{2k} (\xi Lw)^k = (\xi Lw)^k$.

Since f has k finite moments, we know that

$$\int_0^\infty \left| \frac{(-\xi)^k e^{-\xi}}{k!} (-Lw)^k f(w) \right| dw \leq L^k \frac{k^k e^{-k}}{k!} \int_0^\infty w^k f(w) dw < \infty.$$

Therefore,

$$\begin{aligned}
\text{Var } X_t^L &= \int_0^\infty e^{-v} f\Big(\frac{v}{L}\Big) dv \\
&= \int_0^\infty L e^{-wL} f(w) dw \\
&= L\int_0^\infty f(w)dw - L^2\int_0^\infty w f(w)dw + L^3\int_0^\infty \frac{w^2}{2!} f(w)dw \\
&\quad - \ldots + L^{k+1}\int_0^\infty \frac{\xi^k e^{-\xi}}{k!} w^k f(w)dw.
\end{aligned}$$

These are our correction terms.

3.4 Magnitude of Rate Constants

In this section, we consider how the magnitude of the rate constant affects the variance of a linear chain. Although these results do not involve time scaling of the input, they could possibly be used in proving the time-scaling results for the non-linear case. The below theorem gives insight into how the steepness of the slope affects variance. This could be used in making linear approximations of non-linear functions and proving time-limiting results for the non-linear case.

We begin by considering the linear case and we let $0 < \alpha_1 < \alpha_2$.

$$\xrightarrow{\xi_{t/L}} X_1 \xrightarrow{\alpha_1}$$

$$\xrightarrow{\xi_{t/L}} X_2 \xrightarrow{\alpha_2}$$

Interestingly, in the system with the smaller rate constant (compared to the system with the larger rate constant), the variance of the species concentration is less, but the variance of the flux is greater.

Theorem 3.4.1. *Assume $0 < \alpha_1 < \alpha_2$. Let $\mathbb{E}\xi = I$ and let*

$$\begin{aligned} X_1'(t) &= -\alpha_1 X_1(t) + \xi(t) \\ X_2'(t) &= -\alpha_2 X_2(t) + \xi(t) \end{aligned}$$

If ξ is an Ornstein-Uhlenbeck process, then

1. *Var $\alpha_1 X_1 <$ Var $\alpha_2 X_2$*
2. *Var $X_1 >$ Var X_2*

Proof. We will first prove item (1). Consider

$$\frac{d}{dt}(\alpha_1 X_1 - I)^2 = 2(\alpha_1 X_1 - I) \cdot \alpha_1 X_1'(t) = 2\alpha_1(\alpha_1 X_1 - I)(-\alpha_1 X_1 + \xi).$$

Integrating both sides, taking the expectation, and then differentiating, we have

$$\frac{d}{dt}\mathbb{E}(\alpha_1 X_1 - I)^2 = 2\alpha_1 \mathbb{E}[(\alpha_1 X_1 - I)(-\alpha_1 X_1 + \xi)].$$

Let X_1^* be the stationary solution. We know that $\mathbb{E}\alpha_1 X_1^* = I$. By stationarity,

$$2\alpha_1 \mathbb{E}[(\alpha_1 X_1^* - I)(-\alpha_1 X_1^* + \xi)] = 0.$$

Next, we expand the binomial and rearrange the terms:

$$\begin{aligned} -\alpha_1^2 \mathbb{E}(X_1^*)^2 + \alpha_1 \mathbb{E} X_1^* \xi + \alpha_1 I \mathbb{E} X_1^* - I\mathbb{E}\xi &= 0 \\ -\alpha_1^2 \mathbb{E}(X_1^*)^2 + \alpha_1 \mathbb{E} X_1^* \xi + I^2 - I^2 &= 0 \\ \mathbb{E}(\alpha_1 X_1^*)^2 &= \alpha_1 \mathbb{E} X_1^* \xi \end{aligned} \tag{3.5}$$

Similarly,

$$\mathbb{E}(\alpha_2 X_2^*)^2 = \alpha_2 \mathbb{E} X_2^* \xi \tag{3.6}$$

Since $\mathbb{E}\alpha_1 X_1^* = \mathbb{E}\alpha_2 X_2^* = I$, it will suffice to show that $\alpha_1 \mathbb{E} X_1^* \xi < \alpha_2 \mathbb{E} X_2^* \xi$ in order to complete our proof that Var $\alpha_1 X_1 <$ Var $\alpha_2 X_2$. Well,

$$\begin{aligned}
\mathbb{E}[\alpha_1 X_1^* \xi - \alpha_2 X_2^* \xi] &= \mathbb{E}\bigg[\int_{-\infty}^{t} \big(\alpha_1 e^{-\alpha_1(t-s)} - \alpha_2 e^{-\alpha_2(t-s)}\big)\xi(s)\xi(t)ds \bigg] \\
&= \int_{-\infty}^{t} \big(\alpha_1 e^{-\alpha_1(t-s)} - \alpha_2 e^{-\alpha_2(t-s)}\big)\mathbb{E}\xi(s)\xi(t)ds
\end{aligned}$$

We now make use of our assumption that ξ is an Ornstein-Uhlenbeck process with covariance $\mathbb{E}\xi(s)\xi(t) = \frac{\sigma^2}{2\theta} e^{-\theta(t-s)}$ where θ is the drift and σ is the diffusion. Returning to our equation above, we have

$$\begin{aligned}
\mathbb{E}[\alpha_1 X_1^* \xi - \alpha_2 X_2^* \xi] &= \int_{-\infty}^{t} \big(\alpha_1 e^{-\alpha_1(t-s)} - \alpha_2 e^{-\alpha_2(t-s)}\big)\frac{\sigma^2}{2\theta} e^{-\theta(t-s)} ds \\
&= \frac{\sigma^2}{2\theta} \int_{-\infty}^{t} \big(\alpha_1 e^{-(\alpha_1+\theta)(t-s)} - \alpha_2 e^{-(\alpha_2+\theta)(t-s)}\big) ds \\
&= \frac{\sigma^2}{2\theta} \bigg(\frac{\alpha_1}{\alpha_1+\theta} - \frac{\alpha_2}{\alpha_2+\theta} \bigg) \\
&= \frac{\sigma^2}{2} \bigg(\frac{\alpha_1 - \alpha_2}{(\alpha_1+\theta)(\alpha_2+\theta)} \bigg) \\
&< 0
\end{aligned}$$

since $\alpha_1 < \alpha_2$. Thus, Var $\alpha_1 X_1 <$ Var $\alpha_2 X_2$.

We next prove item (2). Returning to equations 3.5 and 3.6 from above, we see that they can be rewritten

$$\begin{aligned}
\mathbb{E}(X_1^*)^2 &= \frac{1}{\alpha_1} \mathbb{E} X_1^* \xi \\
\mathbb{E}(X_2^*)^2 &= \frac{1}{\alpha_2} \mathbb{E} X_2^* \xi
\end{aligned}$$

by dividing through by α_1^2 and α_2^2, respectively. Using similar steps as in the proof of the first part, we calculate

$$\begin{aligned}
\mathbb{E}\left[\frac{1}{\alpha_1}X_1^*\xi - \frac{1}{\alpha_2}X_2^*\xi\right] &= \int_{-\infty}^{t}\left(\frac{1}{\alpha_1}e^{-\alpha_1(t-s)} - \frac{1}{\alpha_2}e^{-\alpha_2(t-s)}\right)\mathbb{E}\xi(s)\xi(t)ds \\
&= \frac{\sigma^2}{2\theta}\int_{-\infty}^{t}\left(\frac{1}{\alpha_1}e^{-(\alpha_1+\theta)(t-s)} - \frac{1}{\alpha_2}e^{-(\alpha_2+\theta)(t-s)}\right)ds \\
&= \frac{\sigma^2}{2\theta}\left(\frac{1}{\alpha_1(\alpha_1+\theta)} - \frac{1}{\alpha_2(\alpha_2+\theta)}\right) \\
&> 0
\end{aligned}$$

since $\alpha_1 < \alpha_2$. Thus, Var $X_1 >$ Var X_2.

□

4

Single Species Complex (SSC) Systems

One class of chemical reaction networks studied by David Anderson, [3], are linear single species complex (SSC) systems. These are defined as follows. Consider a network where each chemical reaction converts one substrate into one product. There is a corresponding directed graph for such a given chemical network. Each node corresponds to a chemical species, and a directed edge corresponds to a reaction. For instance, $X_i \to X_j$ is the reaction converting species X_i into species X_j.

Definition 4.0.1. *A graph is* **weakly reversible** *if whenever there is a directed path form X_i to X_j, then there is also a directed path from X_j to X_i. A system with non-zero input is called* **weakly reversible** *if it is weakly reversible in the above sense and there is at least one non-zero output.*

Assume that the graph is connected, and that the reaction rate is proportional to the reactant species (mass action kinetics) with rate constant $b_{i,j} \geq 0$. The concentrations of the substrates are governed by linear differential equations.

Definition 4.0.2. *A* **single species complex network** *is a network that:*

1. *is weakly reversible*
2. *has mass action kinetics*
3. *consists of single linkage class*
4. *each complex is a single substrate*

It is from the last property that the name is derived. An example is pictured in Figure 4.1.

4.1 Background

Consider a weakly reversible SSC system with mass action kinetics. Throughout this chapter, we let $\vec{I} = (I, 0, \ldots, 0)$ and $\vec{\xi}_{t/L} = (\xi_{t/l}, 0, \ldots, 0)$.. This system can be represented

$$\frac{d}{dt}\vec{X}(t) = A\vec{X}(t) + \vec{I} + \vec{\xi}\Big(\frac{t}{L}\Big)$$

where A is the matrix of rate constants for the system.

Dave Anderson proved in [3] that

$$\vec{X}(t) = \int_{-\infty}^{t} e^{A(t-s)}\vec{I}ds + \int_{-\infty}^{t} e^{A(t-s)}\vec{\xi}\Big(\frac{s}{L}\Big)ds$$

is a stationary solution to the system. Assuming ξ has mean zero, the concentration m_i of the ith species X_i can be represented:

$$\begin{aligned} X_i^L &= \int_{-\infty}^{t} Ie^{A(t-s)}e_1 \cdot e_i ds + \int_{-\infty}^{t} \xi\Big(\frac{s}{L}\Big)e^{A(t-s)}e_1 \cdot e_i ds \\ \mathbb{E}(x_i^L) &= \int_{-\infty}^{t} Ie^{A(t-s)}e_1 \cdot e_i ds \\ m_i &= \int_{-\infty}^{t} Ie^{A(t-s)}e_1 \cdot e_i ds \end{aligned}$$

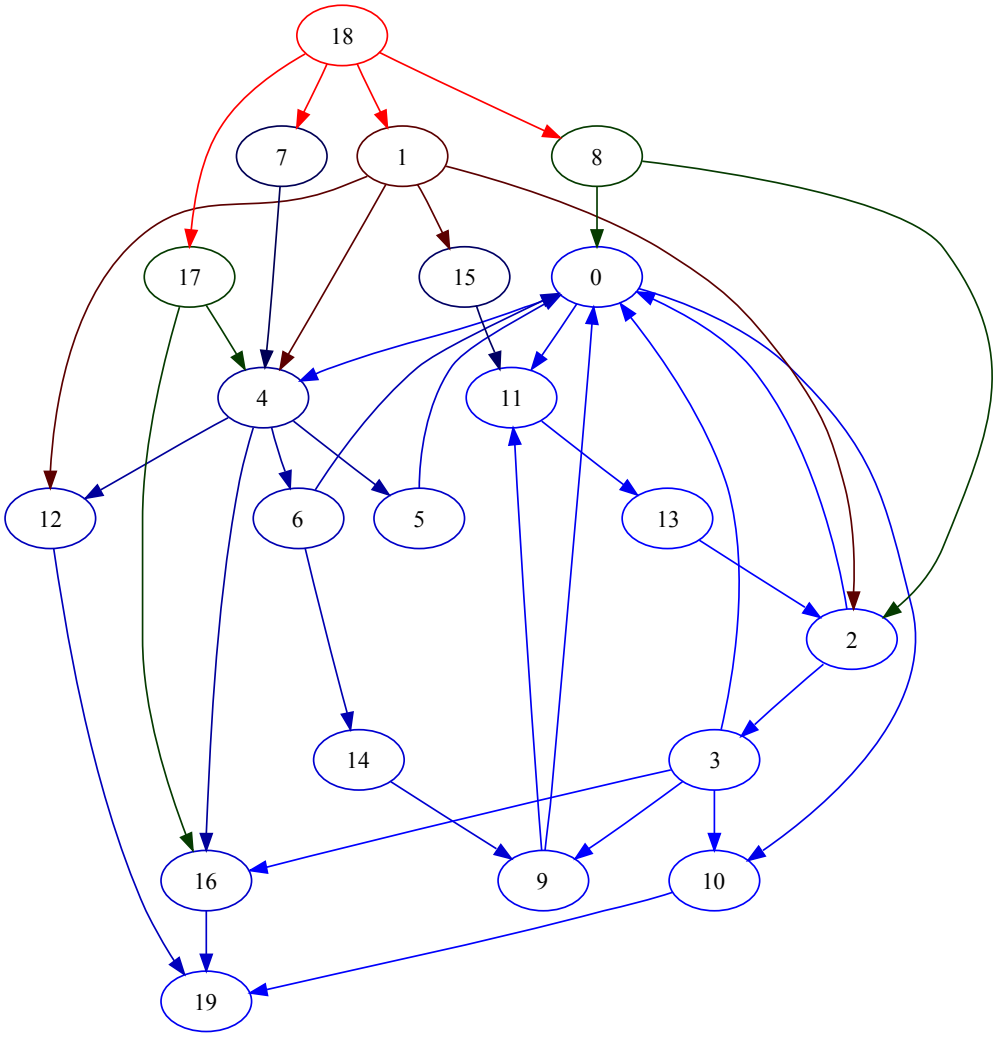


FIGURE 4.1: In this example of an SSC system, the species are color-coded in a gradient by their variance, with red being the most variance and blue being the least variance.

Furthermore, by a lemma to Feinberg's Deficiency Zero Theorem, we know that the eigenvalues of A have strictly negative real parts. We will use this in our proof of Theorem 4.2.1.

Lemma 4.1.1. *(Anderson [3]) If a linear SSC system with m substrates and at least one nonzero input is weakly reversible, then*

1. *The differential equations have a unique equlibrium which is globally asymptotically stable and in* $\mathbb{R}^m_{>0}$.

2. *The eigenvalues of A have strictly negative real parts.*

3. *For all vectors* $v \in \mathbb{R}^m_{\geq 0}, e^{At}v \cdot e_j \geq 0$ *for all* j.

This lemma is surprising in that the hypotheses are related to the network of the system while the conclusion is related to its dynamical properties.

4.2 Results for SSC Systems

We are now ready to consider the limiting behavior of the variance in time-scaled SSC systems. As in chapter 3, we make the following assumption on ξ.

Assumption 4.2.1. *let* ξ *be a stochastic process such that*

1. $\xi_t \geq -1$ *and* $\mathbb{E}\xi = 0$

2. $\mathbb{E}(\xi_t\xi_s) = f(|t-s|)$ *where* $f \geq 0$ *is measurable and bounded with* $\lim_{x\to\infty} f(x) = 0$.

Then our previous time-limiting results for chains are also true for any species within the network, up to a normalization factor.

Theorem 4.2.1. *For any species $X_{i,t}^L$ in an SSC system with input ξ meeting assumption 4.2.1,*

$$\begin{aligned}\lim_{L\to\infty} Var\ X_{i,t}^L &= \left(\frac{m_i}{I}\right)^2 f(0) = \left(\frac{m_i}{I}\right)^2 Var\ \xi \\ \lim_{L\to 0} Var\ X_{i,t}^L &= 0\end{aligned}$$

Proof. The variance of species X_i is:

$$\begin{aligned}\text{Var } X_i^L &= \mathbb{E}\left[\int_{-\infty}^{t} \xi_{s/L} e^{A(t-s)} ds\right]^2 \\ &= \mathbb{E}\left[\int_{-\infty}^{t} e^{A(t-s)}\xi_{s/L} ds \int_{-\infty}^{t} e^{A(t-r)}\xi_{r/L} dr\right] \\ &= \int_{-\infty}^{t}\int_{-\infty}^{t} \mathbb{E}[\xi_{s/L}\xi_{r/L}](e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i) ds dr \\ &= \int_{-\infty}^{t}\int_{-\infty}^{t} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i) ds dr\end{aligned}$$

In order to apply the Dominated Convergence Theorem, we first define the following functions:

$$\begin{aligned}g_{i,L}(s,r) &= f(\frac{1}{L}|s-r|)(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i) \\ g(s,r) &= M(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i)\end{aligned}$$

By lemma 4.1.1, the eigenvalues of the matrix of rate constants A, have strictly negative real parts. Since f is measurable, $g_{i,L}$ is measurable on $(-\infty, t] \times (-\infty, t]$.

Also, g is integrable:

$$\begin{aligned}\int_{-\infty}^{t}\int_{-\infty}^{t} g(s,r)dsdr &= M\int_{-\infty}^{t}\int_{-\infty}^{t}(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr \\ &= M\Big(\int_{-\infty}^{t}(e^{A(t-s)}e_1\cdot e_i)ds\Big)^2 \\ &= M\Big(\frac{m_i}{I}\Big)^2\end{aligned}$$

Thus, because $g_L \leq g$ and g is integrable, we can use the Lebesgue Dominated Convergence Theorem to take the limits as L goes to zero and as L goes to infinity. Recall that

$$\text{Var } X_i^L = \int_{-\infty}^{t}\int_{-\infty}^{t} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr$$

By the Dominated Convergence Theorem, we obtain:

$$\begin{aligned}\lim_{L\to\infty}\text{Var } X_i^L &= \lim_{L\to\infty}\int_{-\infty}^{t}\int_{-\infty}^{t} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr \\ &= \int_{-\infty}^{t}\int_{-\infty}^{t}\lim_{L\to\infty}\Big(f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)\Big)dsdr \\ &= \int_{-\infty}^{t}\int_{-\infty}^{t} f(0)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr \\ &= f(0)\Big(\int_{-\infty}^{t}(e^{A(t-s)}e_1\cdot e_i)ds\Big)^2 \\ &= f(0)\Big(\frac{m_i}{I}\Big)^2\end{aligned}$$

Note that the last line follows from the calculation above that

$$m_i = \mathbb{E}(X_i) = \int_{-\infty}^{t} Ie^{A(t-s)}e_1\cdot e_i ds$$

As in our proof of the $L \to 0$ case for simple chains, we will need to break the region of integration into three separate pieces:

$$(-\infty, r-\epsilon] \cup [r-\epsilon, r+\epsilon] \cup [r+\epsilon, t]$$

We calculate the limit of the variance:

$$\begin{aligned}
\lim_{L\to 0} \text{Var } X_i^L &= \lim_{L\to 0} \int_{-\infty}^{t}\int_{-\infty}^{t} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr \\
&= \lim_{L\to 0} \int_{-\infty}^{t} \Bigg[\int_{-\infty}^{r-\epsilon} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)ds \\
&\quad + \int_{r-\epsilon}^{r+\epsilon} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)\Big)ds \\
&\quad + \int_{r+\epsilon}^{t} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)\Big)ds\Bigg]dr \\
&= 0 + \int_{-\infty}^{t}\int_{r-\epsilon}^{r+\epsilon} \lim_{L\to 0} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr + 0
\end{aligned}$$

Define $\lambda = \min |\text{Real}(\lambda_i)|$, where λ_i are the eigenvalues of A.

$$\begin{aligned}
\lim_{L\to 0} \text{Var } X_i^L &\leq \int_{-\infty}^{t}\int_{r-\epsilon}^{r+\epsilon} M(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr \\
&\leq \int_{-\infty}^{t}\int_{r-\epsilon}^{r+\epsilon} Me^{-\lambda(t-s)}e^{-\lambda(t-r)}dsdr \\
&\leq \frac{M}{\lambda}\int_{-\infty}^{t} e^{-\lambda(t-r)}\big(e^{-\lambda(t-r-\epsilon)} - e^{-\lambda(t-r+\epsilon)}\big)dr \\
&\leq \frac{M}{\lambda}\int_{-\infty}^{t} e^{-2\lambda(t-r)}\big(e^{\lambda\epsilon} - e^{-\lambda\epsilon}\big)dr \\
&\leq \frac{M}{2\lambda^2}\big(e^{\lambda\epsilon} - e^{-\lambda\epsilon}\big)
\end{aligned}$$

Since $\epsilon \geq 0$ can be arbitrarily small, $\lim_{L\to 0} \text{Var } X_i^L \leq 0$. □

As the input speeds up, the variance of the flux through any species in the system approaches zero in the limit. As the input slows down, the variance of the flux through any species approaches the variance of the input, up to a normalization factor. This concludes our treatment of the general single species complex system case.

5

Reversible chains

We will next consider reversible chains, which are very useful in modeling chemical reactions:

$$\xrightarrow{I+\xi} X_1 \underset{b_1}{\overset{k_1}{\rightleftharpoons}} X_2 \underset{b_2}{\overset{k_2}{\rightleftharpoons}} \cdots \underset{b_{n-1}}{\overset{k_{n-1}}{\rightleftharpoons}} X_n \xrightarrow{k_n}$$

Reversible chains are a type of SSC network, so our result from the previous section holds. However, we can prove a more specific result involving the net flux at each step in the chain. We will first define a set of variables y_i, $i = 1, \ldots, n$ representing the flow through each node. That is, we define

$$\begin{aligned} y_1 &= k_1 X_1 - b_1 X_2 \\ &\vdots \\ y_{n-1} &= k_{n-1} X_{n-1} - b_{n-1} X_n \\ y_n &= k_n X_n \end{aligned}$$

Differentiating each side and substituting in the equations we have for $\dot{x_i}$, we get

$$\begin{aligned} \dot{y_1} &= k_1(I + \xi - y_1) - b_1(y_1 - y_2) \\ \dot{y_i} &= k_i y_{i-1} - (k_i + b_i)y_i + b_i y_{i+1} \qquad \text{for } 1 < i < n \\ \dot{y_n} &= k_n(y_{n-1} - y_n) \end{aligned} \tag{5.1}$$

We will show that our limiting results also hold for the y_i.

Theorem 5.0.2. *Given the system in 5.1 with stochastic input following assumption 4.2.1,*

$$\begin{aligned} \lim_{L\to\infty} Var\ y_{t,L} &= f(0) = Var\ \xi \\ \lim_{L\to 0} Var\ y_{t,L} &= 0 \end{aligned}$$

Let A be the matrix of rate coefficients:

$$A = \begin{pmatrix} -(k_1 + b_1) & b_1 & & & & \\ k_2 & -(k_2 + b_2) & b_2 & & & \\ & & \ddots & & & \\ & & & k_{n-1} & -(k_{n-1} + b_{n-1}) & b_{n-1} \\ & & & & k_n & -k_n \end{pmatrix}$$

If $e^{A(t-s)}$ is integrable, we can write

$$\vec{y}(t) = k_1 \int_{-\infty}^{t} e^{A(t-s)} \vec{I} ds + k_1 \int_{-\infty}^{t} e^{A(t-s)} \vec{\xi}(s) ds$$

This is the case if all eigenvalues of A have negative real parts.

5.1 Matrix Properties

Define the $j \times j$ matrix for $j = 2, \ldots, n$:

$$A_j = \begin{pmatrix} -(k_{n-j+1} + b_{n-j+1}) & b_{n-j+1} & & & & \\ k_{n-j+2} & -(k_{n-j+2} + b_{n-j+2}) & b_{n-j+2} & & & \\ & & \ddots & & & \\ & & & k_{n-1} & -(k_{n-1} + b_{n-1}) & b_{n-1} \\ & & & & k_n & -k_n \end{pmatrix}$$

We will first prove two lemmas necessary for the proof of Theorem 5.0.2.

Lemma 5.1.1.

$$\mathrm{Det}(A_j) = (-1)^j \prod_{i=1}^{j} k_{n-i+1}$$

for $j = 2, \ldots, n$.

Proof. This formula can be written iteratively as $\mathrm{Det}(A_j) = -k_{n-j+1}\mathrm{Det}(A_{j-1})$ We will use induction. First consider that

$$A_2 = \begin{pmatrix} -(k_{n-1} + b_{n-1}) & b_{n-1} \\ k_n & -k_n \end{pmatrix}$$

So $\mathrm{Det}A_2 = (k_{n-1} + b_{n-1})k_n - b_{n-1}k_n = k_{n-1}k_n$.

$$A_3 = \begin{pmatrix} -(k_{n-2} + b_{n-2}) & b_{n-2} & 0 \\ k_{n-1} & -(k_{n-1} + b_{n-1}) & b_{n-1} \\ 0 & k_n & -k_n \end{pmatrix}$$

We use expansion by minors along the first column to obtain:

$$\begin{aligned} \mathrm{Det}\ A_3 &= -(k_{n-2} + b_{n-2})\mathrm{Det}(A_2) - k_{n-1}\mathrm{Det} \begin{pmatrix} b_{n-2} & 0 \\ k_n & -k_n \end{pmatrix} \\ &= -(k_{n-2} + b_{n-2})\mathrm{Det}(A_2) + k_{n-1}b_{n-2}k_n \\ &= -(k_{n-2} + b_{n-2})k_{n-1}k_n + k_{n-1}b_{n-2}k_n \\ &= -k_{n-2}k_{n-1}k_n \end{aligned}$$

Assume the inductive hypothesis holds for values less than j. Then

$$\mathrm{Det}\ A_{j-1} = -k_{n-j+2}\mathrm{Det}\ A_{j-2}$$

Using expansion by minors along the first column of A_j,

$$\begin{aligned}
\text{Det } A_j &= -(k_{n-j+1} + b_{n-j+1})\text{Det}(A_{j-1}) \\
&\quad - \quad k_{n-j+2}\text{Det}\begin{pmatrix} b_{n-j+1} & 0 & 0 & \dots & 0 \\ k_{n-j+3} & -(k_{n-j+3} + b_{n-j+3}) & b_{n-j+3} & & \\ & & \ddots & & \\ & & & k_n & -k_n \end{pmatrix} \\
&= -(k_{n-j+1} + b_{n-j+1})\text{Det}(A_{j-1}) - k_{n-j+2}b_{n-j+1}\text{Det}(A_{j-2})
\end{aligned}$$

This follows from the fact that b_{n-j+1} is the only non-zero entry in the first row of the minor matrix. By our inductive hypothesis,

$$\begin{aligned}
\text{Det } A_j &= -(k_{n-j+1} + b_{n-j+1})\text{Det}(A_{j-1}) - k_{n-j+2}b_{n-j+1}\text{Det}(A_{j-2}) \\
&= -(k_{n-j+1} + b_{n-j+1})\text{Det}(A_{j-1}) + b_{n-j+1}\text{Det}(A_{j-1}) \\
&= -k_{n-j+1}\text{Det}(A_{j-1})
\end{aligned}$$

This determinant calculation completes our proof. □

Note that $A_n = A$ so the above lemma gives an explicit formula for the determinant of A. Using this formula, we show that the eigenvalues of A have strictly negative real parts. This will also require the use of Geršgorin's Theorem, as stated in [7].

Theorem 5.1.2. *(Geršgorin). Let $A = [a_{i,j}]$ be an n by n matrix. Let*

$$R_i(A) = \sum_{\substack{j=1 \\ j \neq i}}^{n} |a_{ij}|, \quad 1 \leq i \leq n$$

denote the deleted absolute row sums *of A. Then all the eigenvalues of A are located in the union of n discs*

$$\bigcup_{i=1}^{n} \{z \in \mathbb{C} : |z - a_{ii}| \leq R_i(A)\} \equiv G(A)$$

Proof. Let λ be an eigenvalue of A and suppose $Ax = \lambda x$, $x = [x_i] \neq 0$. There is an element of the vector x that has largest absolute value, say $|x_p| \geq |x_i|$ for all $i = 1, 2, \ldots n$, and $x_p \neq 0$. Then the assumption that $Ax = \lambda x$ means that

$$\lambda x_p = [\lambda x]_p = [Ax]_p = \sum_{j=1}^{n} a_{pj} x_j$$

which is equivalent to

$$x_p(\lambda - a_{pp}) = \sum_{\substack{j=1 \\ j \neq p}}^{n} a_{pj} x_j$$

We then apply the triangle inequality to conclude that

$$\begin{aligned} |x_p||\lambda - a_{pp}| &= \Big| \sum_{\substack{j=1 \\ j \neq p}}^{n} a_{pj} x_j \Big| \\ &\leq \sum_{\substack{j=1 \\ j \neq p}}^{n} |a_{pj} x_j| \\ &= \sum_{\substack{j=1 \\ j \neq p}}^{n} |a_{pj}||x_j| \\ &\leq |x_p| \sum_{\substack{j=1 \\ j \neq p}}^{n} |a_{pj}| \\ &= |x_p| R_p \end{aligned}$$

Therefore, $|\lambda - a_{pp}| \leq R_p$ for some p. That is, λ is in a closed disc around a_{pp} of radius R_p. □

We use this theorem in the lemma below.

Lemma 5.1.3. *All eigenvalues of A have negative real parts.*

Proof. We apply Geršgorin's Theorem. All the eigenvalues of A are contained in the union of n discs:

$$\{z : |z + (k_1 + b_1)| \leq b_1\} \cup \left(\bigcup_{i=2}^{n-1} \{z : |z + (k_i + b_i)| \leq k_i + b_i\} \right) \cup \{z : |z + k_n| \leq k_n\}$$

Thus, the eigenvalues must either have negative real part or be zero. As defined above, $A_n = A$ our matrix of rate coefficients. Thus, by the previous lemma,

$$\text{Det}(A) = (-1)^n \prod_{i=1}^{n} k_i$$

and for non-zero k_i, zero is not an eigenvalue of A. □

5.2 Results for Reversible Chains

We are now ready to prove theorem 5.0.2.

Proof. We can express the solution to equation 5.1 as:

$$\vec{y}(t) = k_1 \int_{-\infty}^{t} e^{A(t-s)} \vec{I} ds + k_1 \int_{-\infty}^{t} e^{A(t-s)} \vec{\xi}(s) ds$$

The variance of y_i is:

$$\begin{aligned}
\text{Var } y_{i,L} &= k_1^2 \mathbb{E}\left[\int_{-\infty}^{t} \xi_{\frac{s}{L}} e^{A(t-s)} ds \right]^2 \\
&= k_1^2 \mathbb{E}\left[\int_{-\infty}^{t} e^{A(t-s)} \xi_{\frac{s}{L}} ds \int_{-\infty}^{t} e^{A(t-r)} \xi_{\frac{r}{L}} dr \right] \\
&= k_1^2 \int_{-\infty}^{t} \int_{-\infty}^{t} \mathbb{E}[\xi_{\frac{s}{L}} \xi_{\frac{r}{L}}] (e^{A(t-s)} e_1 \cdot e_i)(e^{A(t-r)} e_1 \cdot e_i) ds dr \\
&= k_1^2 \int_{-\infty}^{t} \int_{-\infty}^{t} f\Big(\frac{1}{L}|s-r|\Big) (e^{A(t-s)} e_1 \cdot e_i)(e^{A(t-r)} e_1 \cdot e_i) ds dr
\end{aligned}$$

As in the proof for SSC systems, let

$$\begin{aligned} g_{i,L}(s,r) &= k_1^2 f(\frac{1}{L}|s-r|)(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i) \\ g(s,r) &= k_1^2 M(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i) \end{aligned}$$

Since f is measurable, $g_{i,L}$ is measurable on $(-\infty,t]\times(-\infty,t]$. It is necessary that the eigenvalues of A have negative real parts for g to be integrable on $(-\infty,t]\times(-\infty,t]$:

$$\begin{aligned} \int_{-\infty}^{t}\int_{-\infty}^{t} g(s,r)dsdr &= k_1^2 M\int_{-\infty}^{t}\int_{-\infty}^{t}(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i)dsdr \\ &= k_1^2 M\bigg(\int_{-\infty}^{t}(e^{A(t-s)}e_1 \cdot e_i)ds\bigg)^2 \end{aligned}$$

By our earlier calculation that $I = \mathbb{E}(y_i) = k_1 I\int_{-\infty}^{t} e^{A(t-s)}e_1 \cdot e_i ds$, we are able to simplify:

$$\begin{aligned} \int_{-\infty}^{t}\int_{-\infty}^{t} g(s,r)dsdr &= k_1^2 M\bigg(\frac{1}{k_1}\bigg)^2 \\ &= M \end{aligned}$$

Because $g_L \leq g$ and g is integrable on $(-\infty,t]\times(-\infty,t]$, we can use the Lebesgue Dominated Convergence Theorem to take the limits as L goes to zero and as L goes to infinity.

Recall

$$\text{Var } y_{i,L} = k_1^2\int_{-\infty}^{t}\int_{-\infty}^{t} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1 \cdot e_i)(e^{A(t-r)}e_1 \cdot e_i)dsdr$$

By the Dominated Convergence Theorem, we obtain:

$$\begin{aligned}
\lim_{L\to\infty} \text{Var } y_{i,L} &= k_1^2 \lim_{L\to\infty} \int_{-\infty}^{t}\int_{-\infty}^{t} f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr \\
&= k_1^2 \int_{-\infty}^{t}\int_{-\infty}^{t} \lim_{L\to\infty}\Big(f\Big(\frac{1}{L}|s-r|\Big)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)\Big)dsdr \\
&= k_1^2 \int_{-\infty}^{t}\int_{-\infty}^{t} f(0)(e^{A(t-s)}e_1\cdot e_i)(e^{A(t-r)}e_1\cdot e_i)dsdr \\
&= k_1^2 f(0)\Big(\int_{-\infty}^{t}(e^{A(t-s)}e_1\cdot e_i)ds\Big)^2 \\
&= f(0)
\end{aligned}$$

Similarly, we can again use the Dominated Convergence Theorem to calculate the limit as L approaches 0, also making use of the requirement that $\lim_{x\to\infty} f(x) = 0$. In conclusion, the two limits are:

$$\begin{aligned}
\lim_{L\to\infty} \text{Var } y_{t,L} &= f(0) = \text{Var } \xi \\
\lim_{L\to 0} \text{Var } y_{t,L} &= 0
\end{aligned}$$

□

6

Conclusion

In this thesis, I have proved analytic results of how the variance of reaction rates within a system compares to the variance of the input when the input is on a different time scale than the reaction kinetics within the network.

Hormonal and neural inputs vary on a scale of seconds or minutes; inputs from meals and circadian rhythms vary on a scale of hours or days; and long term environmental changes (such as diet, disease, and pollution) vary on a scale of years. Here, we have considered the limiting behavior of networks in which the input is on a different time scale compared to the reaction kinetics within the network. The volume of these systems is large enough that they may be represented as systems of differential equations. The input is constantly fluctuating, so the systems do not reach a static equilibrium.

I have proved results regarding the limiting behavior of the variance of the flux in simple chains, single species complex networks, and reversible chains with time-scaled stochastic input as the input speeds up and slows down. In all cases, as the input fluctuates more and more quickly, the variance of species within the system approaches zero. The intuitive idea behind this is that the concentrations of species

within a system are found by integrating the input. With quickly fluctuating input, the fluctuations cancel each other out as they are averaged over. As the input fluctuates more and more slowly, the variance of the species approaches the variance of the input, up to a normalization factor. The intuitive reason for this is that although the system is not able to relax completely to equilibrium, the input is changing so slowly that the system is always approximately at equilibrium.

There are several directions which would be interesting to pursue for future exploration of this topic. One set of questions relates to the pathwise distribution of the fluxes in the limit. In the fast case, the flux is approaching a constant, but what is its distribution around that constant? Similarly, in the slow case, the pathwise behavior of the flux is approaching the path of the input, but what is its distribution around that path? In the linear cases discussed in Chapters 4 and 5, determining the eigenvalues and eigenvectors of the matrices of rate constants may give more insight into the behavior of the system, and of its distribution and speed as it approaches the limit.

Another area of interest would be to extend these results to non-linear systems. A simple case to begin with would be that of Michaelis-Menten kinetics. The Michaelis-Menten equation is frequently used in biology to describe irreversible enzymatic reactions. As substrate concentrations increase, the reaction velocity increases. For very large concentrations of the substrate, the enzyme approaches saturation and the reaction asymptotically approaches a maximum velocity. See Figure 6.1.

We could consider the following system:

$$\xrightarrow{\xi_{t/L}} X \xrightarrow{F(X)}$$

$$dX_t^L = \xi_{t/L}dt - F(X_t^L)dt \tag{6.1}$$

where $F(X) = \frac{V_{max}X}{K_m+X}$ for some positive constants V_{max}, K_m.

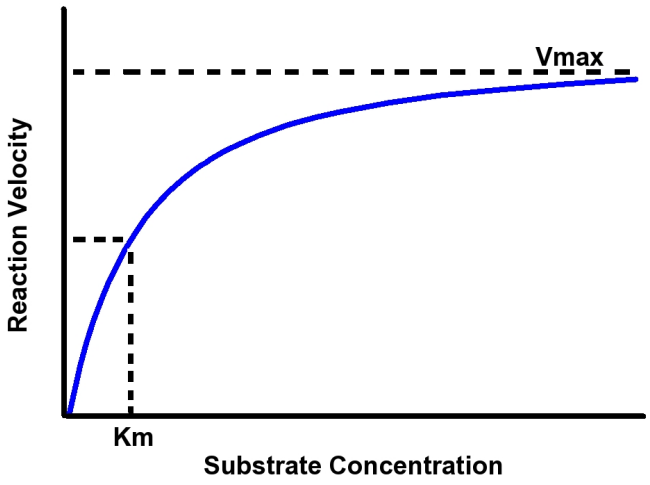


FIGURE 6.1: Michaelis-Menten Kinetics.

In the fast case, it may be possible to use a comparison argument to prove the limiting result, after first bounding the Michaelis-Menten curve by a linear function. The steepness argument from Section 3.4 could be relevant here. For the slow case, an asymptotic expansion of the function F could possibly be used. Since F, along with its inverse and derivatives, has a reasonably nice form, it is expected that an asymptotic expansion could be obtained to describe the limiting behavior of the system in 6.1.

Another area of interest is the application of control theory to biochemical reaction networks. Complex biochemical systems, such as one-carbon cell metabolism (see [13] and [16]), receive amino acids from food as inputs and have a range of health implications. For instance, deficits in glutathione have been implicated in a variety of diseases including Alzheimer's disease, Parkinson's disease, cardiovascular disease, cancer, Down syndrome and autism (see [17]). Control theory may be useful in discovering ways to correct deficiencies or other irregular metabolic profiles. It could give us valuable insight into how the concentrations of various substrates can be controlled by modifying inputs. Stochastic control theory may provide insight

into how to reduce the fluctuations in concentration of different substrates as the input varies.

Bibliography

[1] D.F. Anderson, G. Craciun, and T.G. Kurtz. Product-form stationary distributions for deficiency zero chemical reaction networks. 2009.

[2] D.F. Anderson and J.C. Mattingly. Propagation of fluctuations in biochemical reaction systems, II: Nonlinear chains. *IET Systems Biology*, 1:313–325, 2007.

[3] D.F. Anderson, J.C. Mattingly, H.F. Nijhout, and M.C. Reed. Propagation of fluctuations in biochemical systems, I: Linear SSC networks. *Bulletin of Mathematical Biology*, 69:1791–1813, 2007.

[4] W. E, D. Liu, and E. Vanden-Eijnden. Nested stochastic simulation algorithms for chemical kinetic systems with multiple time scales. *Journal of Computational Physics*, 21:158–180, 2007.

[5] R. Heinrich and T.A. Rapoport. Mathematical analysis of multienzyme systems II. steady state and transient control. *Biosystems*, 7:130–136, 1975.

[6] H.F. Nijhout HF, M.C. Reed, and C.M. Ulrich. A day in the life of cell metabolism. *Journal of Biological Theory*, 2:124–127, 2007.

[7] R.A. Horn and C.R. Johnson. *Matrix Analysis*. Cambridge University Press, 1985.

[8] H. Kacser and J.A. Burns. The control of flux. *Symp. Soc. Exp. Biol.*, 27:65–104, 1973.

[9] T. G. Kurtz. The relationship between stochastic and deterministic models for chemical reactions. *J. Chem. Phys.*, 57:2976–2978, 1972.

[10] H.J. Kushner. *Stochastic Stability and Control*. Academic Press, 1967.

[11] J.R. Leigh. *Functional Analysis and Linear Control Theory*. Academic Press, 1980.

[12] H.F. Nijhout, M.C. Reed, D.F. Anderson, J.C. Mattingly, S.J. James, and C.M. Ulrich. Long-range allosteric interactions between the folate and methionine cycles stabilize dna methylation reaction rate. *Epigenetics*, 1:81–87, 2006.

[13] H.F. Nijhout, M.C. Reed, P. Budu, and C.M. Ulrich. A mathematical model of the folate cycle. *J. Biol. Chem.*, 279:55008–55016, 2004.

[14] G.A. Pavliotis and A.M. Stuart. *Multiscale Methods: Averaging and Homogenization*. Springer, 2008.

[15] S.A. Petronella, R.L. Thomas, J.A. Stone, R.M. Goldblum, and E.G. Brooks. Clearing the air: A model for investigating indoor air quality in texas schools. *Journal of Environmental Health*, 67:35–42, 2005.

[16] M.C. Reed, H.F. Nijhout, R. Sparks, and C.M. Ulrich. A mathematical model of the methionine cycle. *J. Theor. Biol.*, 226:33–43, 2004.

[17] M.C. Reed, R.L. Thomas, J. Pavisic, S.J. James, C.M. Ulrich, and H.F. Nijhout. A mathematical model of glutathione metabolism. *Theo. Biol. & Med. Modeling*, 8:8, 2008.

[18] R.C. Rhoades and R.L. Thomas. When abelian groups split. *Rose-Hulman Mathematical Technical Report Series*, 03-01, 2003.

[19] C.E. Rohrs, J.L. Mesa, and D.G. Schultz. *Linear Control Systems*. McGraw-Hill Inc., 1993.

[20] H.L. Royden. *Real Analysis*. Prentice Hall, third edition, 1988.

Biography

Rachel Lee Thomas was born on June 12, 1983 in Boston, Massachusettes and grew up in Galveston, Texas. She graduated Phi Beta Kappa from Swarthmore College in May 2005 with a B.A. in Mathematics and minors in Computer Science and Linguistics. Rachel received her M.A. and Ph.D. in Mathematics from Duke University in December 2006 and May 2010, respectively. During her time at Duke, she was supported by a James B. Duke Fellowship, a Howard Hughes Fellowship, teaching assistantships, and a Research Triangle Institute- Health Solutions internship.

Rachel has co-authored the papers "A Mathematical Model of Glutathione Metabolism" [17], "Clearing the Air: A Model for Investigating Indoor Air Quality in Texas Schools" [15], and "When Abelian Groups Split" [18]. She is currently working on a model of the cost-effectiveness of initiating HIV treatment earlier. Rachel was on the organizing committee for the 3rd and 4th annual Graduate Student Probability Conferences, which received rave reviews, and she served as a Mathematics Graduate Student Representative for 2007-2008. Rachel has accepted a job as a quantitative analyst at Exelon in Kennett Square, Pennsylvania.